OBSTETRICS

Noninvasive prenatal screening for aneuploidy: positive predictive values based on cytogenetic findings

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OBJECTIVE: We sought to determine the positive predictive value (PPV) of noninvasive prenatal screening (NIPS) for various aneuploidies based on cases referred for follow-up cytogenetic testing. Secondarily, we wanted to determine the false-negative (FN) rate for those cases with a negative NIPS result.

STUDY DESIGN: We compared the cytogenetic findings (primarily from chromosome analysis) from 216 cases referred to our laboratories with either a positive or negative NIPS result, and classified NIPS results as true positive, false positive, true negative, or FN. Diagnostic cytogenetic testing was performed on the following tissue types: amniotic fluid (n = 137), chorionic villi (n = 69), neonatal blood (n = 6), and products of conception (n = 4).

RESULTS: The PPV for NIPS were as follows: 93% for trisomy (T) 21 (n = 99; 95% confidence interval [CI], 86–97.1%), 58% for T18 (n = 24; 95% CI, 36.6–77.9%), 45% for T13 (n = 11; 95% CI, 16.7–76.6%), 23% for monosomy X (n = 26; 95% CI, 9–43.6%), and 67% for XXY (n = 6; 95% CI, 22.3–95.7%). Of the 26 cases referred for follow-up cytogenetics after a negative NIPS result, 1 (4%) was FN (T13). Two cases of triploidy, a very serious condition but one not claimed to be detectable by the test providers, were among those classified as true negatives.

CONCLUSION: T21, which has the highest prevalence of all aneuploidies, demonstrated a high true-positive rate, resulting in a high PPV. However, the other aneuploidies, with their lower prevalence, displayed relatively high false-positive rates and, therefore, lower PPV. Patients and physicians must fully understand the limitations of this screening test and the need in many cases to follow up with appropriate diagnostic testing to obtain an accurate diagnosis.

Key words: aneuploidy, cytogenetics, noninvasive prenatal screening

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Noninvasive prenatal screening (NIPS) for fetal aneuploidy was introduced into clinical practice in November 2011. Obstetricians have rapidly adopted this testing, and patients have welcomed this option due to its lack of fetal morbidity and mortality.

NIPS started as a screen for only trisomy 21 (T21) and was rapidly expanded to include other common aneuploidies for chromosomes 13 (T13), 18 (T18), X, and Y. Many publications and presentations at national and international scientific meetings have been presented by the companies performing this screening,[1-4] which are intentionally selected to have a high frequency of samples with aneuploid results. These initial studies measured the success of their testing based on sensitivity and specificity for each aneuploidy. More recently, studies were performed from the perspective of an obstetric setting[5,6]; these studies have a large normal population with relatively few aneuploid cases. However, there have been few published data from the perspective of a cytogenetics laboratory.[7-9] All studies have reported very high specificities and sensitivities, with low false-positive (FP) rates. The positive predictive value (PPV) (or negative predictive value) can be derived from the specificity and sensitivity data presented in earlier publications[10]; however, until more recently, these have not been specifically addressed.[2,11,12]

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All authors work (or were working at the time of inception of this study) for a company (J.M.M., E.K.D., L.M., A.A., C.T., D.P.-A., S.A., R.T.K.) or academic institution (A.M.C.) that performs prenatal cytogenetic testing.

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Sensitivity and specificity describe characteristics of a test and measure its validity; ie, does the test measure what it is supposed to measure? It is most desirable for a screening test to be highly specific (few FP) and highly sensitive (few false negatives [FN]). In the case of NIPS, a low FP rate would alleviate much anxiety on the part of the expectant parents and also reduce the number of invasive procedures performed on non-aneuploid pregnancies. A low FN rate would reduce the unexpected birth of a baby with an aneuploidy after a negative NIPS result. The FP rate also plays a role in calculating the PPV. By contrast to sensitivity and specificity, a population-based PPV tells us the percentage of patients with a positive test who actually have the disease,[13] and is the measure that answers the pretest question of interest to physicians and patients: Given an NIPS result that shows a high risk for a given fetal aneuploidy, what is the chance that the fetus is affected?

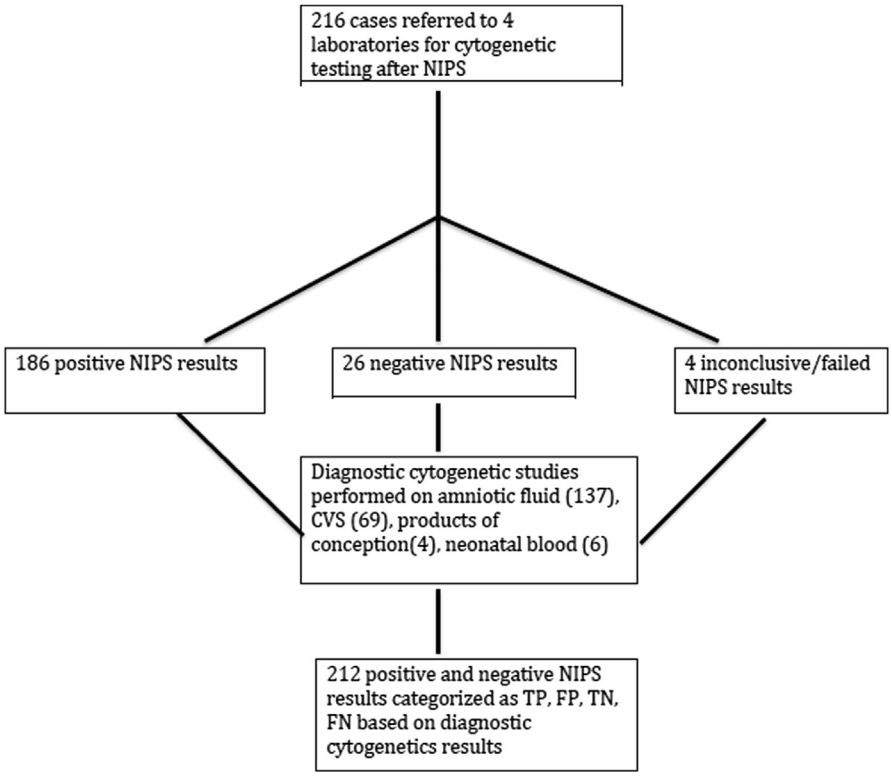
Materials and Methods

We reviewed all of the cases received during an approximate 3-year period (November 2011 through October 2014) in 4 cytogenetics laboratories (GeneDx, Gaithersburg, MD; Stanford Hospital and Clinics, Palo Alto, CA; GenPath, Elmwood Park, NJ; the Genetics Center GenPath, Smithtown, NY) in which the referring physician noted on the test request form that there had been prior NIPS performed on that pregnancy. When available, we noted clinical indications in addition to the specimen type collected for follow-up cytogenetic testing, the company performing the NIPS, and maternal age. Signed patient consent forms included a clause stating that information obtained from their testing in our laboratories could be used for publication purposes providing that patient anonymity was preserved.

NIPS testing was performed by 4 different companies (Sequenom, Natera, Ariosa, Verinata), each of which has company-specific language for the reporting of an abnormal result. Any result classified as "high risk" (Ariosa, Natera), "aneuploidy detected" (Verinata), or "positive" (Sequenom) was considered "positive" for purposes of this study. Furthermore, in many cases, the actual NIPS result was not provided and we used the information regarding test result as reported by the referring physician. In some cases, information regarding the company performing NIPS was not provided. We compared the NIPS results to those obtained by aneuploidy fluorescence in situ hybridization, chromosome analysis, and/or microarray. Chromosome analysis was performed on all but 2 cases and was considered the gold standard to which the NIPS result was compared and used for the determination of whether the NIPS would be classified as true positive (TP), FP, true negative (TN), or FN. Chromosome analysis of chorionic villus sampling (CVS) was reported on cultured mesenchymal core cells only. In the 2 cases where chromosome analysis was not performed, microarray analysis was the diagnostic result to which the NIPS results were compared and rated. The PPV (#TP/[#TP + #FP]×100) was calculated for each aneuploidy. The binomial probability distribution was used to calculate 95% confidence intervals (CI). See the Figure for overview of study.

Follow-up information on phenotype or genotype after delivery was not available for most cases and, therefore, not included.

FIGURE
Study flowchart



CVS, chorionic villus sampling; *FN*, false negative; *FP*, false positive; *NIPS*, noninvasive prenatal screening; *TN*, true negative; *TP*, true positive.

Meck. Comparison of NIPS and cytogenetic findings. Am J Obstet Gynecol 2015.

Results

We reviewed data on 216 cases referred for follow-up cytogenetic testing after a positive or negative NIPS result. Four of these cases were at increased risk for >1 T or monosomy (M): T13, T18, and T21; T18 and XXY; T18 and XXX; and M13, M18, M21, and MX. The gestational age at the time of referral for diagnostic cytogenetic testing ranged from 10-28 5/7 weeks. Of the cases referred to our laboratories after NIPS, 90% were high risk